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Original Article

SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF TADALAFIL IN PHARMACEUTICAL FORMS

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ABSRACT

Objective: To develop and validate simple and reproducible spectrophotometric methods for the determination of Tadalafil (TDF) in pure and pharmaceutical form.

Methods: Methods (A and B) were developed, method A is based on oxidation of (TDF) with a known excess amount of Ce(IV) then estimation of the unreacted amount of Methyl orange (MO) dye at 507 nm, Method B is based on the oxidation of (TDF) with excess N-bromosuccinamide then estimation the amount of Indigo carmine (IC) at 610 nm.

Results: The methods were linear in the concentration ranges 18–60 and 10–55 µg/ml with correlation coefficients of 0.993 and 0.992 and limits of detection LOD of 10.5 and 5.3 µg/ml for the two methods respectively. The proposed methods were applied for the determination of the drug in pharmaceutical formulations with recovery and relative standard deviations of 97% ± 1.4 and 98% ± 1.1 for the two methods.

Conclusion: the developed methods are equally accurate, precise and reproducible compared to the official methods.

Keywords: Tadalafil, Spectrophotometric determination, Oxidation, Drug formulation.

INTRODUCTION

Tadalafil (TDF) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), used in the management of erectile dysfunction. Chemically tadalafil is pyrazino- [1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol- 5-yl) 2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR) (Figure 1). It is listed in the Merck Index [1] and Martindale. Extensive literature survey revealed that the determination of (TDF) in pure and dosage forms are [2] not official in any pharmacopoeia and therefore, require much more investigation. Several analytical methods that have been reported for the estimation of (TDF) in biological fluids or pharmaceutical dosage forms are liquid chromatography [3-5] and spectrophotometry [6,7]. The well-established spectrophotometric method employs direct UV spectrophotometric estimation of (TDF) [6]. Other methods are based on ion-pair complex formation between basic compounds and an anionic dye such as bromocresol purple (BCP) and methyl orange (MO) [7-10], At a specific pH, the ion-pair is extracted into an organic solvent, which is immiscible with water, and the concentration of the resulting ion pair in the organic phase is determined spectrophotometrically. In the present investigation, we report the development of accurate, reproducible, less time consuming and adequately sensitive validated spectrophotometric methods for the determination of (TDF) based on its oxidation with excess amount of Ce(IV) and NBS in acidic media, and the residual amount of the oxidants bleach Methyl orange and Indigo carmine dyes respectively. After that the residual amount of these dyes correlate with the amount of (TDF) in the original solution. The proposed methods were applied to the determination of (TDF) in tablets dosage form. No interference was observed in the assay of (TDF) from common excipients in levels found in dosage form. These methods are validated by statistical data and can be adopted by the pharmaceutical laboratories for industrial quality control.

MATERIALS AND METHODS

Apparatus

Spectro UV-Vis Double Beam (UVD- 3500, Labomed.Inco) was used with spectral bandwidth of **1.0 nm**, wavelength accuracy **± 0.3 nm** (with automatic wavelength correction), wavelength range (**190 nm-1100 nm**), wavelength reproducibility **± 0.2 nm** and a pair of **1-cm** matched quartz cells was used to measure absorbance of the resulting solution.

Materials

All chemicals used were of analytical reagent grade and the solvents were spectroscopic grade. Double distilled water was used wherever required.

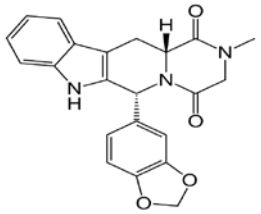

Fig. 1: Chemical structure of Tadalafil

Tadalafil tablets (Cialis), labeled to contain 20 mg Tadalafil per tablet.

The stock solution of 220 µg/ml (TDF) was prepared in acetonitrile solution and was used to prepare different standard solutions. Standard solution of Tadalafil was prepared by dissolving 0.022 g of the drug in 100 ml acetonitrile. An aqueous solutions of (MO) (Aldrich; 200 µg/ml) and (IC) (Merck; 200 µg/ml) were prepared by dissolving the appropriate weight of the dye in a very small volume of water and then made up to 100 ml in a calibrated flask.

Ce(IV) solution was prepared by dissolving 0.25 g of ammonium cerium sulfate (Aldrich) in 0.5 M sulfuric acid solution, NBS solution was prepared by dissolving 0.12 g of N-bromosuccinamide (Aldrich) in distilled water.

The stock solutions of dyes were allowed to stand at room temperature for a few weeks without any significant decay.

Construction of calibration curves

Method A: Different volumes (0-3 ml) of standard (TDF) (220 µg/ml) Solutions were pipette into 10 ml volumetric flasks, then 2.5

ml of 1000 µg/ml Ce(IV) solution and 2.0 ml of 0.5 M sulfuric acid solution were added the mixture was then shacked and kept for 10 minutes, after that 2.5 ml of the (MO) (200 µg/ml) then the solution was made up to the 10.0 ml with distilled water. The absorbance was then measured at (507 nm) after 10 minutes.

Method B: The same method above was performed as in method A except using 1ml of 1200 µg/ml NBS solution as oxidant and 3.0 ml of 200 µg/ml of (IC) dye solutions were used, the absorbance of the final solutions were measured at (610 nm). For the two methods a proportional increase in the absorbance for the two dyes is observed with increasing concentration of (TDF) which is obvious in (Fig. 2 and Fig. 3).

Optimum reaction conditions

The optimum conditions for color development in each method were established by varying the parameters one at a time, keeping the others fixed and observing the effect produced on the absorbance of the colored species for methods A and B. In a series of experiments, the volumes of both dyes were varied using the constant concentrations of both (TDF) and the selected oxidants, the results which are shown in (Fig. 4 and Fig. 5) revealed that the optimum volumes of both Methyl orange and Indigo carmine dyes were 2.5 and 3 ml of the given concentrations respectively. A Ce(IV) concentration of 100 µg/ml was found to bleach the color due to 200 µg/ml (MO) and A NBS concentration of 120 µg/ml was used to bleach the solution of 200 µg/ml of (IC). For both methods the Absorbance was monitored at 25°C with time which showed that the oxidation reaction is fast and complete in five minutes, and contact times up to 8 minutes had no effect on the absorbance of dyes.

Procedures for drug formulations

An amount of finely ground tablets equivalent to 2.0 mg of (TDF) was accurately weighed, dissolved in appropriate amount of distilled water and transferred to a 100-ml volumetric flask, the flask was sonicated for about 20 minutes, finally the volume was made up to the mark. The content was kept aside for 5 min, and filtered using 0.45µm GHP filter paper. The first 10-ml portion of the filtrate was discarded and a suitable aliquot was used for the assay as described under General analytical procedure for the proposed method or using HPLC method.

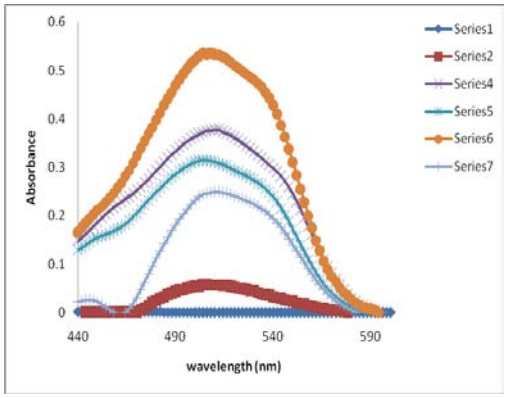

Fig. 2: Linearity spectra using Method A.

RESULTS AND DISCUSSION

Tadalafil undergoes fast oxidation reaction with strong oxidizing agents.

It shows no absorption band in the visible region which makes it difficult to be determined directly using simple spectrophotometric methods. So we suggest two simple and inexpensive procedures for the determination of (TDF) in pure and pharmaceutical preparations based on treating (TDF) solutions with an excess amount of oxidizing agent, then the residual amount of oxidant bleaches certain dye, so that the remaining amount of dye can be determined spectrophotometrically.

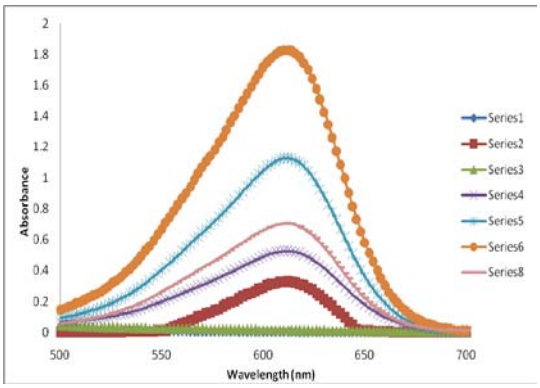

Fig. 3: Linearity spectra using Method B

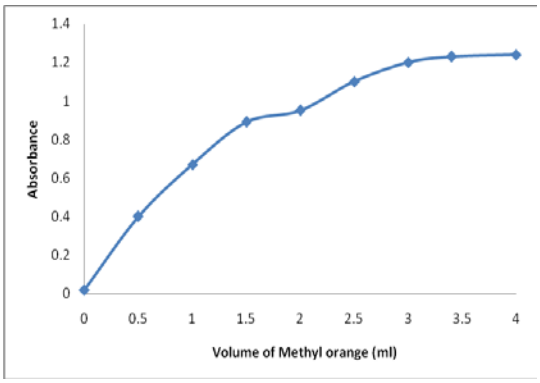

Fig. 4: Effect of variation of volume of Methyl orange dye on the absornance at 507 nm.

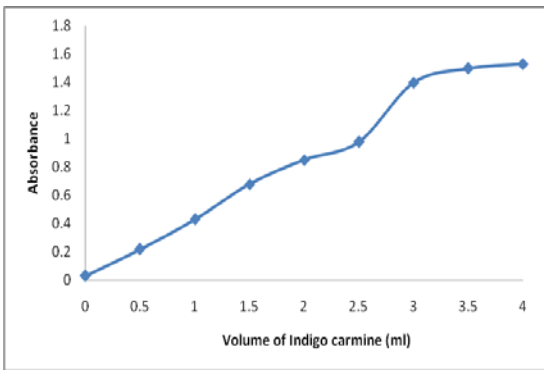

Fig. 5: Effect of variation of volume of Indigo carmine dye on the absornance at 660 nm.

In method A. Ce(IV) in sulfuric acid was used as oxidizing agent and (MO) was used as a dye the absorbance was measured at 507 nm.

In method B. NBS in sulfuric acid was used as oxidizing agent and (IC) was used as the dye which has a maximum absorption at 610 nm. Preliminary experiments were performed to fix the upper concentrations of the oxidants that could be used to maintain excess amounts.

Method validation

Analytical parameters

Calibration curves for (TDF) determination using the proposed methods A and B were constructed by plotting absorbance *vs.* concentration using the optimized amounts of oxidants and dyes. The intercepts, slopes, and correlation coefficients were calculated

using the method of least squares. Beer's law is obeyed over concentration ranges of 18-60 µg/ml for (Method A) and 10-55 µg/ml for (Method B). The mean molar absorptivity (ε), limit of detection (LOD = 3s/k) and limit of quantitation (LOQ = 10s/k) were calculated, where s is the standard deviation of replicate determinations in the absence of analyte under the same conditions as sample analysis and k is the slope. The LOD were 10.5 and 5.3 µg/ml using methods A and B respectively, these statistical results are shown in (Table 1).

Table 1: Statistical analysis of calibration graphs and analytical data in the determination of Tadalafil by Methods (A and B) (n = 6).

Parameters	Proposed Method	
	A	B
Wavelengths λ_{max} (nm)	507	610
Slope (*b*)	0.031	0.032
Intercept (*a*)	0.043	0.09
Correlation coefficient (r^2)	0.993	0.992
Beer's law limits (µg/ml)	18-60	10-55
Sandell, *s* sensitivity (ng/cm)	10.52	23.9
LOD (µg/ml)	10.5	5.3
LOQ (µg/ml)	15.6	7.7
R.S.D.%	0.77	1.3
Molar absorptivity ε, (l mol^{-1} cm^{-1})	10464	14922

Application to drug formulation

The suggested method were applied successfully for the determination of Tadalafil in commercial tablets, Statistical comparison of the accuracy and precision of the proposed methods with an HPLC method [11] was performed using Student's t-tests at a 95% confidence level. The t-values did not exceed the theoretical values; there is no significant difference in accuracy or precision between the proposed and the official method as shown in (Table 2).

Table 2: Comparison between the proposed method and the standard method

Drug	Proposed Method		Standard Method		
	Amount taken (µg/ml)	Recovery ± RSD%	Amount taken (µg/ml)	Recovery ± RSD%	t-value
Method A	50	97% ± 1.4	50	98% ±0.9	0.85
Method B	50	98% ± 1.1	50	97% ±1.3	0.56

Tabulated student t-value at 95% confidence level and 6 degrees of freedom. (2.44)

CONCLUSION

Tadalafil was determined in a two simple spectrophotometric methods, the first method is based on oxidation the drug by Ce(IV) oxidant in the presence of Methyl orange while the second method used NBS and Indigo carmine dye. The methods were simple, rapid, and accurate and they were validated and compared to standard methods.

CONFLICT OF INTERESTS

Declared None

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